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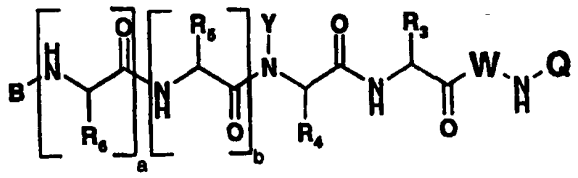
P6 P5 P4 P3 P2 P1



(I)

(57) Abstract

Compound of formula (I) active against the Hepatitis C virus, wherein B is an acyl derivative; a is 0 or 1; R_6, when present, is carboxy(lower)alkyl; b is 0 or 1; R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl; Y is H or C_{1-6} alkyl; R_4 is C_{1-10} alkyl; R_3 is C_{1-10} alkyl; W is $-NH-CH(R_2)-C(O)-$, wherein R_2 is C_{1-6} alkyl; C_6 or C_{10} aryl; C_{7-16} aralkyl; or carboxy(lower)alkyl; or W is a proline derivative; Q is a group of the formula $-Z(R_1)-C(O)-R_{13}$, wherein Z is CH or N; R_1 is C_{1-6} alkyl or C_{1-6} alkenyl both optionally substituted with thio or halo; and R_{13} is an activated carbonyl substituent, or Q is a phosphonate group of the formula $-CH(R_1)-P(O)R_{15}R_{16}$ wherein R_{15} and R_{16} are independently C_{6-20} aryloxy; and R_1 is as defined above.

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After 60 min pre-incubation at 30°C, 20 µL of substrate solution (50 mM Tris-HCl, pH 8, 0.5 M Na_2SO_4, 50 mM NaCl, 0.1 mM EDTA, 665 µM Succ-AAA-pNA) were added to each well and the reaction was further incubated at 30°C for 60 min after which time the absorbance was read on the UV Thermomax® plate reader. Rows of wells were allocated for controls (no inhibitor) and for blanks (no inhibitor and no enzyme).

The sequential 2-fold dilutions of the inhibitor solution were performed on a separate plate by the liquid handler using 50 mM Tris-HCl pH 8, 50 mM NaCl, 0.1 mM EDTA, 0.02% Tween-20, 15% DMSO. All other specificity assays were performed in a similar fashion.

The percentage of inhibition was calculated using the formula:

$$[1-((UV_{inh}-UV_{blank})/(UV_{ctl}-UV_{blank}))] \times 100$$

A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc., Cary, N.C.).

Example 21

Tables of compounds

The following tables list IC_{50} values of compounds representative of the invention.

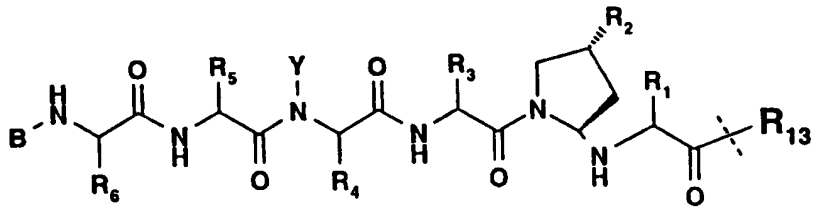
The following abbreviations are used:

IC_{50}: The concentration required to obtain 50% inhibition in the NS3 protease/NS4A cofactor peptide radiometric assay according to Example 19.

HLE: The concentration required to obtain 50% inhibition in the human leukocyte elastase assay; **PPE**: The concentration required to obtain 50% inhibition in the porcine pancreatic elastase assay; **Other**: Figures unmarked indicate the concentration required to obtain 50% inhibition in the bovine pancreatic α-chymotrypsin assay; figures marked with ** indicate the concentration required to obtain 50% inhibition in the human liver cathepsin B assay; **MS**: Mass spectrometric data (MH^+ from FAB); **AAA**: amino acid analysis data expressed in % peptide recovery; **Acpr**: 1-amino-cyclopropylcarboxylic acid; **Acpe**: 1-amino-cyclopentylcarboxylic acid; **Abu**: aminobutyric acid; **Chg**: cyclohexylglycine (2-amino-2-cyclohexyl-acetic acid); **Hyp**: 4*(R)*-hydroxyproline; **Hyp(4-Bn)**: 4*(R)*-benzyloxyproline; **Pip**: pipecolic acid; **Tbg**: *tert*-butylglycine; **Ac**: acetyl; **Bn**: benzyl; **O-Bn**: benzyloxy; **DAD**: 3-carboxypropionyl; and **DAE**: 4-carboxybutyryl.

Table 1

P6 P5 P4 P3 P2 P1



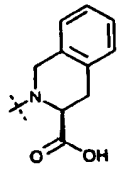
cpd	B	P6	P5	P4	P3	R_2	R_1	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH^+)	AAA (%)
101	Ac	Asp	D-Glu	Ile	Val	O-Bn	ethyl	CF_3	9.4	<1.2			857.4	
102	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	CF_2CF_3	0.21				921	99.2
103	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	C(O)NH-Bn	0.023				936	
104	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	H	0.14	7	8	8	803	115
105	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	NH_2	54				818	108
106	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	CH_2CH_2-Ph	5.4	16			908	107.8
107	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	$NHCH_2Ph$	3				908	100.8
108	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	*(S)*-NH-CH(Me)Ph	0.71	3	>300	>300	922	107
109	Ac	---	---	Chg	Val	O-Bn	propyl	C(O)-NHBn	23	2			718.3	
110	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl		8				(MH^-) 753.5	

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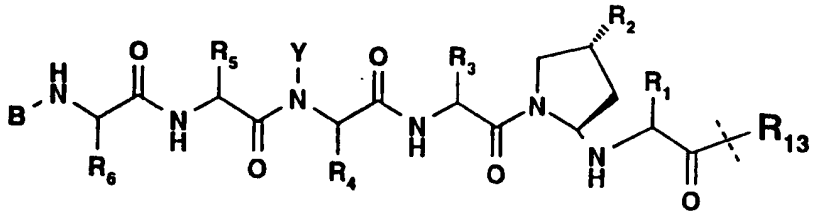
Table 1

P6 P5 P4 P3 P2 P1



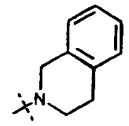
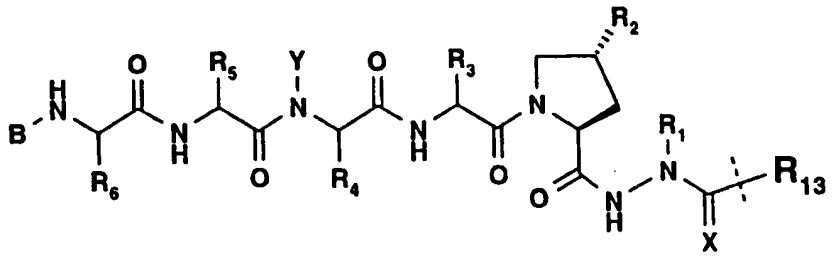
cpd	B	P6	P5	P4	P3	R_2	R_1	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH^+)	AAA (%)
111	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl		20					
112	Ac	Asp	D-Glu	Ile	Val	H	propyl	C(O)-NH-Bn	2	0.03	<0.06	10.3	814.4	104.4
113	Ac	Asp	D-Glu	Ile	Val	H	propyl	CF_2-CF_3	12.8	0.07	<0.06	18		
114	Ac	Asp	D-Glu	Ile	Val	H	propyl	CF_3	23.5	0.05	0.2	4.4	749.3	106.7
115	Ac	Asp	D-Glu	Ile	Val	H	propyl	C(O)NH Bn	0.66	0.11	<0.06	30	814	99.4
116	Ac	---	---	Chg	Val	O-Bn	propyl	C(O)NH-CH_2-4-pyridine	25					

Table 2

P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R_2	R_1	X	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)		MS (MH^+)	AAA (%)
201	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	$NHCH_2$-C(O)OEt	3.9	27.4	168		905.2	
202	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	CH_2CH_2-Ph	0.63	5.5			908.4	
203	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	$NHCH_2$-Ph	0.59				909.6	
204	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	*(R)*-NH-CH(Me)Ph	4.2				923.6	
205	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	*(S)*-NH-CH(Me)Ph	0.078	5.1	4.1		923.6	93.4
206	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	OCH_2Ph	0.79	<0.6	<0.6		910	95.6
207	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	$NHCH_2$-C(O)OH	3.75				877.1	106.5
208	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	CH_3	14.5				818.2	101.9
209	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	NH_2	20.5				819.3	100.6
210	Ac	Asp	D-Glu	Ile	Val	O-Bn	Butyl	O	*(S)*-NH-CH(Me)Ph	0.085	4			937.5	95.4
211	Ac	Asp	D-Glu	Ile	Val	O-Bn	Butyl	O	NH_2	47				833	84

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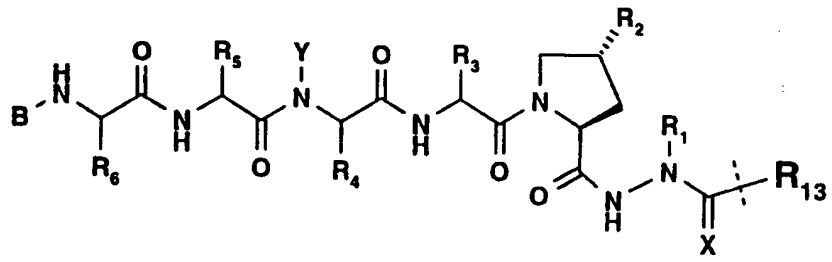
Table 2

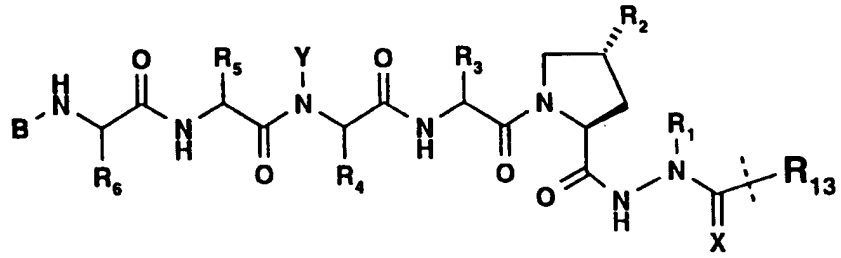
P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R_2	R_1	X	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)		MS (MH^+)	AAA (%)
212	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	*(S)*-NH CH(Me)-naphtyl	0.58	0.4			974.3	98.9
213	Ac	Asp	D-Glu	Ile	Val	O-Bn	Ethyl	O	*(S)*-NH-CH(Me)Ph	0.079	36			909.9	103.3
214	Ac	Asp	D-Glu	Ile	Val	O-Bn	Propyl	O	*(S)*-NH-CH(Et)Ph	0.44				937.5	
215	Ac	---	---	Chg	Val	O-Bn	Propyl	O	*(S)*-NH-CH(Me)Ph	45	5			705.5	95.8
216	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	*(R)*-CH (OH) Ph	9.6				(MH^-) 908.5	
217	Ac	Asp	D-Glu	Ile	Val	H	propyl	O	*(S)*-NH-CH(Me)Ph	1.04				803.4	93.2
218	Ac	Asp	D-Glu	Ile	Val	O-Bn	isopentyl	O	*(S)*-NH-CH(Me)Ph	3.3				951.5	99.5
219	Ac	Asp	D-Glu	ile	Val	O-Bn	pentyl	O	*(S)*-NH-CH(Me)Ph	0.43	151			951.5	
220	HOOC $(CH_2)_2$-C(O)	---	D-Asp	Ile	Val	H	propyl	O	*(S)*-NH-CH(Me)Ph	6.9				(MH^-) 744.5	97.5
221	Ac	Asp	D-Glu	Ile	Val	O-Bn	Me	O	*(S)*-NH-CH(Me)Ph	0.52	168			895	94
222	Ac	Asp	D-Glu	Ile	Val	O-Bn	$(CH_2)_2$-isopropyl	O	*(S)*-NH-CH(Me)Ph	8.9	>300			951.4	98.2
223	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	$N(CH_3)$-Bn	11				923.5	105.5
224	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	S	NH-Bn	5				(MH^-)	

Table 2

P6 P5 P4 P3 P2 P1



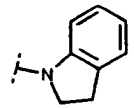
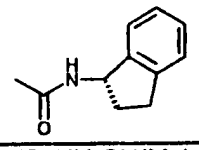
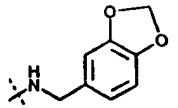
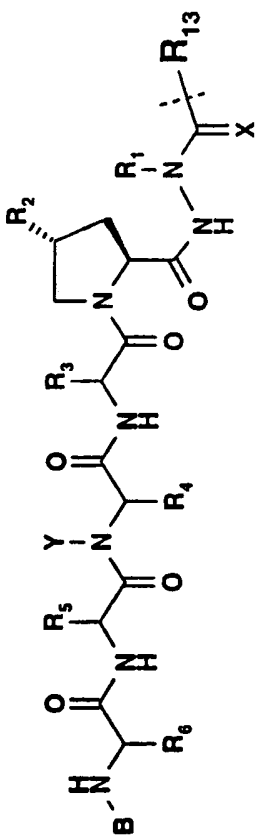
entry #	B	P6	P5	P4	P3	R_2	R_1	X	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)		MS (MH^+)	AAA (%)
														923.4	
225	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	$COCH_3$	13				862.3	102.3
226	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		6.3				921.3	112.8
227	Ac	---	---	Chg	Val	O-Bn	propyl	O	COOH	39.5				(MH^-) 628.3	
228	Ac	Asp	D-Glu	Ile	Val	O-Bn	CH_2-CF_3	O	*(S)*-NH-CH(Me)Ph	0.63				(MH^-) 961.4	
229	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		0.13	3.1			(MH^-) 933.4	94.1
230	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O	*(S)*-NH-CH(Me)	0.36				929.5	100.6
231	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		0.5				953.4	107.3

Table 2

P6 P5 P4 P3 P2 P1



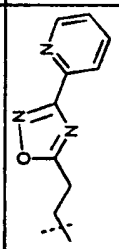
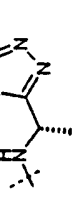
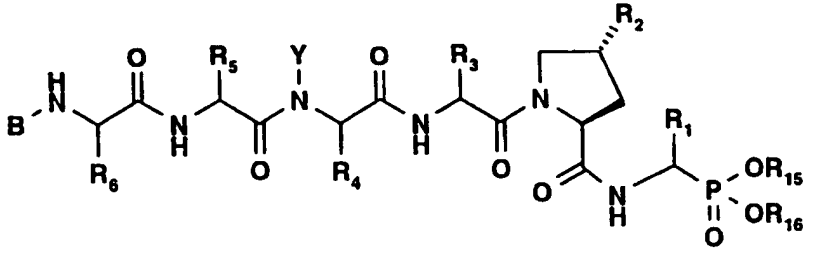
entry #	B	P6	P5	P4	P3	R_2	R_1	X	R_{13}	IC_{50} (μM)	HLE (μM)	PPE (μM)		MS (MH^+)	AAA (%)
232	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		3.2				977.4	96.9
233	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O		1.5				(MH^-) 913.5	
234	Ac	Asp	D-Glu	Ile	Val	O-Bn	CH_2-$CH=CH_2$	O	N-benzyl	3.7				907.5	

Table 3

P6 P5 P4 P3 P2 P1



entry #	B	P6	P5	P4	P3	R_2	R_1	R_{15}	R_{16}	IC_{50} (μM)	HLE (μM)	PPE (μM)	OTHER (μM)	MS (MH^+)	AAA (%)
301	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O-Ph	O-Ph	0.029	<0.6	<0.6	3 >300	1007	86.6
302	Ac	Asp	D-Glu	Ile	Val	O-Bn	propyl	O-Ph	O-Ph	26				1007	

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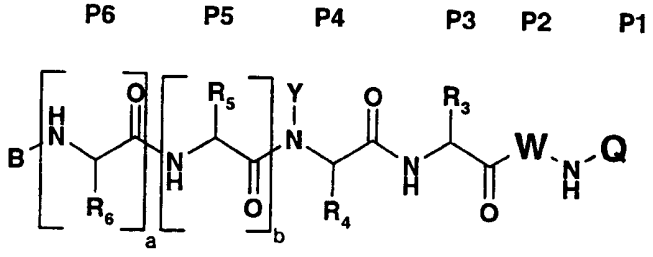
What is claimed is:

1. A compound of formula I:



(I)

wherein **B** is an acyl derivative of formula R_{11}-C(O)- wherein R_{11} is C_{1-10} alkyl optionally substituted with carboxyl; or R_{11} is C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with a C_{1-6} alkyl;

a is 0 or 1;

R_6, when present, is carboxy(lower)alkyl;

b is 0 or 1;

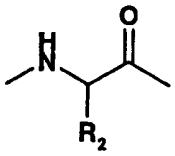
R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl;

Y is H or C_{1-6} alkyl;

R_4 is C_{1-10} alkyl; C_{3-10} cycloalkyl;

R_3 is C_{1-10} alkyl; C_{3-10} cycloalkyl;

W is a group of formula II:



Formula II

wherein R_2 is C_{1-10} alkyl or C_{3-7} cycloalkyl optionally substituted with carboxyl; C_6 or C_{10} aryl; or C_{7-16} aralkyl; or